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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 10/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/856,470	HAGBERG ET AL.	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2 and 4-8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2, 4-8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This action is written in response to applicant's correspondence submitted 7/27/04. Claims 2, 4, 5, and 6 were amended and claims 7-8 were added. Claims 2 and 4-8 are pending. Applicant's amendments and arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections not reiterated in this action have been withdrawn. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action. **This action is final.**

Claim Rejections - 35 USC § 112- New Matter

2. The previously set forth rejection of claims 5 and 6 under 35 U.S.C. 112, first paragraph, as containing new matter is WITHDRAWN in view of the amendment to the claims which cancelled the new matter.

Claim Rejections - 35 USC § 112

3. The previously set forth rejection of claims 2 and 4-6 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is WITHDRAWN in view of applicant's amendments to the claims.

4. Claims 2 and 4-8 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

This is a rejection for new matter.

The addition of the limitation "where lysine is located at position 153 of" to the method of claim 2 is new matter. Likewise, the method of claim 7 which recites this limitation is new matter. Claim 5 depends from claim 2 and is rejected for the same reason. Applicant refers to page 7, line 11 of the specification for support for the amendment. This portion of the specification states "Detection of Lys153Arg Substitiution in Myostatin Exon-2." This provides basis for the actual language added to the claim. However, it does not provide basis to combine this language with a method as recited in claim 2 or claim 7. The specification does not teach that a lysine at position 153 of the second exon of the myostatin gene is in any way associated with an improvement in cholesterol levels after extensive exercise training, as is set forth in the instant claims. With regard to the claimed method, the specification teaches only that "subjects with the myostatin exon 2 '12' genotype increased their plasma HDL-C and HDL2-C levels with exercise training substantially more than subjects with the myostatin exon 2 '11' genotype (p. 8, lines 17-19)." The specification does not, however, define how the "12" and "11" genotypes relate to the polymorphism. These are arbitrary genotype identifiers that are not defined within the specification with regard to the particular alleles of the myostatin Lys153Arg substitution. Therefore, the claims are rejected as containing new matter.

The addition of the limitation "where arginine is located at position 153 of" to the method of claim 4 is new matter. Likewise, the method of claim 8 which recites this limitation is new matter. Claim 6 depends from claim 4 and is rejected for the same reason. Applicant refers to

page 7, line 11 of the specification for support for the amendment. This portion of the specification states "Detection of Lys153Arg Substitiution in Myostatin Exon-2." This provides basis for the actual language added to the claim. However, it does not provide basis to combine this language with a method as recited in claim 4 or claim 8. The specification does not teach that an arginine at position 153 of the second exon of the myostatin gene is in any way associated with an improvement in diabetes status after extensive exercise training, as is set forth in the instant claims. With regard to the claimed method, the specification teaches only that "subjects with the myostatin exon 2 '11' genotype decreased their glucose areas more than subjects with the myostatin exon 2 '12' genotype (p. 9, lines 23-25)." The specification does not, however, define how the "11" and "12" genotypes relate to the polymorphism. These are arbitrary genotype identifiers that are not defined within the specification with regard to the particular alleles of the myostatin Lys153Arg substitution. Therefore, the claims are rejected as containing new matter.

5. Claims 2 and 4-8 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

This rejection is maintained for amended claims 2 and 4-6 and applied to newly added claims 7-8.

Claim 2 is drawn to a method of improving cholesterol levels in a subject in need of such improvement by identifying a subject with hypercholesteremia having a genotype where lysine is

located at position 153 of the second exon of the myostatin gene and engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject. Claim 5 depends from claim 2 and further defines extensive exercise training as at least 10 single courses of exercise over an exercise period of from about 50 to 400 days. Claim 7 is similar to claim 2 but recites that the exercise training is for nine months.

Claim 4 is drawn to a method for improving diabetes status in a subject by identifying a subject with diabetes having a genotype where arginine is located at position 153 of the second exon of the myostatin gene and engaging the subject in extensive exercise training for a period of time sufficient to improve the cholesterol levels in the subject. Claim 6 depends from claim 4 and further defines extensive exercise training as at least 10 single courses of exercise over an exercise period of from about 50 to 400 days. Claim 8 is similar to claim 4 but recites that the exercise training is for nine months.

The claimed methods both rely on the establishment of a relationship between particular alleles in the second exon of the myostatin gene and a particular phenotype (i.e. the ability to improve cholesterol levels with extensive exercise or the ability to improve diabetes status with extensive exercise). The prior art is silent with respect to polymorphisms in the human myostatin gene. However, the state of the art with regard to the establishment of such a relationship between a polymorphism and a phenotype is highly unpredictable. After a screening assay identifies polymorphisms, it is unpredictable whether any such polymorphisms would be associated with any phenotypic trait, such as a disease state or a physiological state. For example, Hacker et al. were unable to confirm an association between a gene polymorphism and ulcerative colitis in a case where prior studies suggested such a relationship would exist since the

relationship had been identified in a different population (Gut, 1997, Vol. 40, pages 623-627). Even in cases where an association between a particular gene and a disease state is known to exist, such as with the LPL gene and heart disease risk or the β-globin gene and sickle cell anemia, researchers have found that when using SNP (single nucleotide polymorphism analysis) it was difficult to associate SNPs with disease states or to even identify key genes as being associated with disease (Pennisi, Science, 281 (5384):1787-1789). Further, Ferrell *et al.* in a 1999 paper were unable to establish a relationship between a polymorphism in exon 2 of the myostatin gene (K153R) and muscle mass response to strength training. This paper is published after the filing of the provisional applications from which this application depends, but nonetheless highlights the unpredictability of establishing a relationship between even this particular myostatin polymorphism and a phenotype.

The specification contains examples which refer to the observed genotypes using codes "11" and "12." The specification, however, fails to define what these codes represent, and thus, the examples which may support the claimed invention are largely unclear as to what observations were made with regard to the alleles present since it is not possible to determine from the examples what actual alleles were present in the tested samples. However, even if these genotypes were clearly defined, the specification is not enabling for the practice of the claimed methods.

The data in the specification further highlight the unpredictability within this art area. With regard to methods for improving cholesterol status, the specification and claims assert that patients with a "12" genotype exhibit greater improvements after an extensive exercise routine for nine months. The specification does not define the "12" genotype, however, and particularly

does not state that this genotype means that there is lysine located at position 153 of the second exon of the myostatin gene. Furthermore, the data to support this assertion only represent three people total with the "12" genotype and the standard deviations in the data points given are nearly as large as the average values reported. No statistical analysis is provided, so it is unknown from the data whether a statistically significant correlation was observed. Certainly the ranges of improvement observed for patients with the "12" genotype versus the "11" genotype overlap when the standard deviations are considered. Thus, the data themselves demonstrate that it is not predictable, even once a genotype is observed which patients will exhibit an improvement even after nine months of an extensive exercise regime.

The data regarding an improvement in diabetes status also is widely variant and represents a small sample population. Also, like with the experiments regarding choleserol levels, the genotypes are not defined in the example or elsewhere in the specification. So, though the claims specifically recite observing a genotype where lysine is located at position 153 of the second exon of the myostatin gene, there is no teaching in the specification to relate this finding to the genotypes observed in the example. Further, no statistical analysis is presented to aid in the interpretation of the data. In light of these factors it is impossible to ascertain whether a reliable association has been demonstrated between nine months of an extensive exercise regime and an improvement in diabetes status correlated with a particular phenotype.

Furthermore, it is noted that the claims 2 and 4 encompass "extensive exercise" for any length of time, yet the specification provides only a demonstration of the changes that occur after nine months of endurance exercise training. Claims 5 and 6 require that the "extensive exercise" is at least 10 single courses of exercise over a period from about 10 to about 500 days. However,

the examples in the specification only demonstrate any sort of improvement over a nine month period of time for which any putative relationship is established in the specification is over 9 months- which is much greater than most of the range specifically encompassed by the claims. It is highly unpredictable as to what other shorter lengths of training would be sufficient to improve cholesterol or diabetes status for patients having the "12" or "11" genotypes, as appropriate.

Thus, in light of the nature of the invention, the state of the art, the high level of unpredictability, the lack of clearly defined and analyzed working examples, and the breadth of the claims, it is concluded that undue experimentation would be required to practice the claimed invention.

Response to Remarks

Applicant's arguments regarding the enablement rejection do not address the merits of the rejection as they pertain to the rejected claims, but instead focus on the teachings of the Hacker *et al.* reference. This reference is cited in combination with other references merely to highlight the fact that the estabilishment of an association between a phenotype and a single nucleotide polymorphism is unpredictable. Hacker *et al.* demonstrates that even if a predictive association is observed for a particular polymorphism within one group of people, that same relationship might not hold for another group of people. NO matter which interpretation of the teachign of Hacker *et al.* is agreed upon, the fact remains that the establishment of a relationship between a polymorphism and a particluar phenotype is an entierly empirical technology and there is no art establishe a priori method for predicting such a relationship. This art is a highly unpredictable art.

With regard to the "extensive exercise" portion of the 112 1st paragraph rejection, applicant points out that the specification discusses a number of possible regimes that are considered "extensive exercise." Claims 5 and 6 have been added which specify a time period for exercise. However, some of these encompass periods of time that are much shorter than the nine months of the example, and there is no evidence in the specification that these shorter periords of time might be associated with improvement.

Furthermore, it si noted that the lack of enablement rejection is not predicated solely on the Hacker reference or the "extensive exercise" portions of the claims. Applicant's arguments are directed towards only portions of the rejection. The rejection is based on an analysis of the following factors: the nature of the invention, the state of the art, the high level of unpredictability, the lack of clearly defined and analyzed working examples, and the breadth of the claims (*In re Wands*, 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988). After discussion and analysis of each of these factors, the rejection concludes that it would require undue experimentation to practice the invention. Applicant has not provided any argument or evidence with regard to this total analysis or conclusion. Thus, Applicant's arguments are not sufficient to overcome the rejections of record. The rejection is MAINTAINED.

Conclusion

6. No claims are allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday through Friday, from 9:00 AM until 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached by calling (571) 272-0782.

The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Juliet C. Switzer
Examiner
Art Unit 1634

September 24, 2004